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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,053	10/17/2007	Robert James Nash	PRC-003	4877

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
08/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/578,053	NASH ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1629

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/02/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,18-20,22 and 26-32* is/are pending in the application.

4a) Of the above claim(s) *4,6,10,11,19 and 26-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5, 7-9, 18, 20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/23/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-11, 18-20, 22 and 26-32 are pending.

Claims 4, 6, 10-11, 19 and 26-32 are withdrawn from consideration as being drawn towards a nonelected invention and specie.

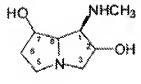
Claims 1, 3, 5, 7-9, 18, 20 and 22 are under consideration in the instant office action.

Election/Restrictions

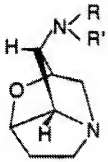
Applicant's election of Group 1 (claims 1,3-11, 18-20 and 22) in the reply filed on 06/02/2011 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of the following compound (example 1, in instant claim 18) is acknowledged.

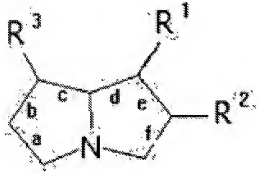
(a) 2,7-dihydroxy-1-methylaminopyrrolizidine:



During the search for the elected specie, other structurally compounds shown below were found, therefore the examination was expanded to include the following species : Loline and norloline shown below and the compound disclosed in instant claim 7 (shown below) Where in R3 is halo, R1 is methylamine and R2 is hydroxy.



	R	R'
Loline	CH_3	H
Norloline	H	H



Claims 1, 3, 5, 7-9, 18, 20 and 22, have been examined to the extent to which they are readable on the elected embodiment and the above identified nonelected species. Since art was found on a nonelected species, subject matter not embraced by the elected embodiment or the above identified nonelected species is therefore withdrawn from further consideration. It has been determined that the entire scope claimed is not patentable. Claims 4, 6, 10-11, 19 and 26-32 are withdrawn from consideration as being drawn to non-elected invention and specie. The restriction

requirement is made final and the claims under consideration in the instant office action are claims 1, 3, 5, 7-9, 18, 20 and 22.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 07/23/2008 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits. See attached copy of the PTO-1449.

Priority

This application is a U.S. National phase application under 35 U.S.C 371 of PCT application non PCT/GB2004/004624, filed November 3rd 2004, and claims foreign priority to United Kingdom application 0324655.9 filed on 11/04/2003.

Claim Rejections - 35 USC § 102(b)

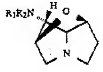
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Powell et al. (US 5,185,028, referenced in the instant IDS)

Instant claims 1 and 3 are drawn towards a pharmaceutical composition comprising an antibacterial aminopyrrolizidine or alkylaminopyrrolizidine compound.

Powell et al disclose N-substituted loline derivatives (aminopyrrolizidine core structure) having the formula (col.2, lines 4-16, reference claim 1).



Powell et al. further discloses composition of their inventive compounds with a carrier wherein the compound is substantially pure (reference claims 10-11). Accordingly claims 1 and 3 are anticipated by Powell et al.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Reddick et al. (US 5,468,486) referenced in the instant IDS.

Instant claims 1 and 3 are drawn towards a pharmaceutical composition comprising an antibacterial aminopyrrolizidine or alkylaminopyrrolizidine compound.

Reddick et al discloses loline (aminopyrrolizidine core structure) in a vaccine formulation as a protein-alkaloid conjugate in a physiologically acceptable carrier (col.2, lines 48-63) wherein the physiologically acceptable carrier include distilled water, normal saline or physiologically buffered saline (col.2, lines 37-39)

Accordingly, claims 1 and 3 are anticipated by Reddick et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

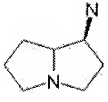
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

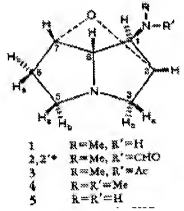
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 7-9, 18, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petroski et al. (Journal of Natural Product, Vol. 52 (4), pages 810-817, 1989, referenced in the instant IDS) in view of Casabuono et al (Journal of ethnopharmacology, volume 57, 1997, pages 1-9) further in view of Patani et al. (Chemical Reviews, volume 96, 1996, pages 3147-3176)

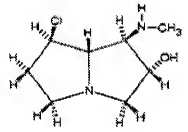
Instant claims 1 and 3 are drawn towards a pharmaceutical composition comprising an antibacterial aminopyrrolizidine or alkylaminopyrrolizidine compound with the core structure



Petroski et al discloses loline alkaloids which are a group of aminopyrrolizidine alkaloids which include loline (compound 1) and norloline (compound 5) shown below (page 810).



Petroski et al. further discloses aminopyrrolizidine compound 9 of the following structure as being an analog of loline called hydroxychlorololine (page 811 and page 817)



9

Petroski et al. does not disclose their compounds to be in a pharmaceutical composition and also fails to disclose the instantly elected compound which has a hydroxy group instead of the chloro position of compound 9 taught by Petroski et al.

However, Casabuono et al. discloses loline-type alkaloids which includes loline and discloses alkaloid extracts as aqueous suspensions administered to mice by i.p injection (page 4, right col. Under toxicological assays) which reads on the pharmaceutical composition limitation of the instant claims. Casabuono et al. further disclose that loline and other loline derivatives have shown some pharmacological activities. Loline and methylloline showed a slight in vivo growth inhibition of Ehrlich carcinoma and other derivatives of loline have been shown to be lethal against three human solid tumor cell lines (page 5, left col., 2nd paragraph).

As such it would have been obvious to one skilled in the art to prepare compositions of compounds such as loline and its derivatives taught by Petroski to test them for a potential therapeutic use motivated by the teachings of Casabuono et al.

With regards to the instantly elected compound 2, 7-dihydroxy-1-methylamionopyrrolizidine, the only difference between the hydroxychlororololine and instantly claimed compound is the presence of a hydroxy group instead of the chlorine group. However, Patani et al. teaches that the Cl group and OH group are bioisosters and one can be substituted by the other without any loss or change in activity (page 3154, right col.). Patani additionally teaches an evaluation study of 4-substitute N- (1,1-dimethylethyl)-3-oxo-4-androsten-17β-carboxamide analogues with hydroxy, thiol, chlorine and bromo substituents at the 4 position to show intermediate inhibitory activity on human type II 5α-reductase activity and from the data it could be inferred that the enzyme has steric and electronic preference at this position , resulting in enhanced potency for the hydroxy and chloro substituted compounds (page 3155, left col, 1st paragraph). Accordingly, it would have been *prima facie* obvious to the skilled artisan to synthesize the instantly claimed compound with a hydroxy substitution on the instead of Cl which is already taught in the art. In view of the close structural similarity between the claimed compound in the instant and the compound taught by Petroski one of ordinary skilled in the art would have been motivated to formulate instantly claimed compound, substituting the chlorine group in Petroski et al.'s compound with other substituents such as OH as the two substituents are taught in the prior art as bioisosters. Also since the instantly elected compound is also a derivative of loline it would have been prima

facia obvious to a skilled artisan to formulate a composition comprising the elected compound with a reasonable expectation of success that they would have a potential pharmacological effect.

In view of the references above, the instantly claimed pharmaceutical compositions comprising aminopyrrolizidine of alkylaminopyrrolizidine compounds would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made. Petroski et al. discloses the instantly claimed compounds as loline and derivatives of loline and as such the instantly claimed compounds were known in the art. . Casabuono et al discloses compositions of loline and its derivatives and further teach that these compounds are known to have pharmacological functions, as such a skilled artisan would be motivated to formulate compositions of similar compounds taught by Petroski et al. with a reasonable expectation of having a physiological activity. Finally, Patani et al. teaches chlorine and hydroxy substituents to be bioisosters and as such it would be obvious to an ordinarily skilled artisan to generate hydroxychlorololine taught by Petroski et al. with a hydroxy substituent thus arriving at the instantly elected compound. As such ordinarily skilled artisan will be imbued with at least a reasonable expectation of success in producing the instantly claimed composition and its utility, especially in the absence of evidence to the contrary.

Conclusion

Claims 1, 3, 5, 7-9, 18, 20 and 22 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached at 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1629